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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/142,524	01/04/99	SUNE	SPO-103

HM22/1012

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EXAMINER	
DIBRINO,M	

ART UNIT	PAPER NUMBER
1644	9

DATE MAILED: 10/12/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic[illegible]
09/142,524	Sone et al
Examiner	**Group Art Unit**
Marianne DiBrino	1644

☒ Responsive to communication(s) filed on *Aug 2, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-9* is/are pending in the application.

Of the above, claim(s) *8 and 9* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. This application is a 371 of PCT/JP97/00740 filed 03/10/97.

2. Applicant's amendment, filed 08/02/99 (Paper No. 7), is acknowledged and has been entered.

Claims 1-9 are pending and being acted upon presently.

3. Applicant's election of the immunotherapeutic agent of claim 3 and SEQ ID NO: 1 with traverse in Paper No. 7 filed 08/02/99 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8 and 9 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The invention being examined in this application is an immunotherapeutic agent comprising a multi-epitope peptide wherein the epitopes are different allergen molecules cry j 1 and cry j 2, wherein said peptide contains SEQ ID NO: 1.

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: the oath does not contain a claim to foreign priority for Application Serial No. 8/80702 JPN, filed March 10, 1996.

5. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

6. Applicants are required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 1-7 are indefinite in the recitation of "substantially react with IgE antibodies" because it is not clear what degree of reactivity with IgE antibodies is acceptable.

The amendments must be supported by the specification so as not to add any new matter.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-5 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rogers et al (Molecular Immunology, Vol. 31 (13) pp 955-966, 1994, entire document) in view of WO 94/01560 (20 January 1994, pages 1-106) and further in view of Hashiguchi et al (Peptide Chemistry, Volume 33, 1996, pages 409-412) or Komiyama et al (Biochemical and Biophysical Research Communications, Volume 201, 1994, pages 1021-1028) or WO 94/11512, and Wallner et al (Allergy, Volume 49, 1994, pages 302-308).

Rogers et al teach a peptide-based immmunotherapeutic agent comprising a linear multi-epitope linear polypeptide with different T cell epitope regions joined to each other, wherein said polypeptide does not substantially react with allergic human IgE, wherein said different T cell epitope regions are derived from two or more different allergen molecules and wherein said polypeptide reacts with peripheral lymphocytes from at least not less than 70% of said population patients sensitive to said allergen(s) (especially Abstract; page 956; Table 2; page 961, column 1, second full paragraph; page 963, column 1, lines 6-9; page 964, column 1, first two full paragraphs; page 964, column 2, lines 24-29 and lines 60-71; page 965, lines 1-2). Rogers et al teach that their approach to a peptide-based immunotherapeutic agent can be generally applicable to the combination of multiple T cell epitope-containing sequences from one or more antigens into a single polypeptide chain, that a single antigen can have multiple T cell epitopes recognized in the atopic human population, and that the polypeptide can also be constructed using T cell epitopes from unrelated antigens or allergens from diverse sources

page 964, lines 60-71 and continuing onto page 965, lines 1-2). Rogers et al inherently teach said immunotherapeutic agent wherein each of the T cell epitope regions shows a positivity index of not less than approximately 100 when measured in a population of patients sensitive to allergen(s) (especially Figure 5 and page 961, column 2, lines 5-17), see below.

Rogers et al do not teach said immunotherapeutic agent supra wherein the T cell epitope regions are comprise different allergen molecules that are cedar pollen allergens Cry j 1 and Cry j 2. Rogers et al do not teach said immunotherapeutic agent wherein a site that is processed in the antigen-presenting cells is inserted between each of the T cell epitope regions, and wherein said site is an arginine dimer (R-R) or a lysine dimer (K-K). Rogers et al do not teach said agent wherein said peptide contains an epitope restricted by at least one HLA-Class II molecule selected from those recited in instant claim 7.

The WO 94/01560 document teaches linear polypeptides comprising at least two different T cell epitope regions from Cry j 1 joined to each other which do not substantially react with allergic human IgE (especially Abstract, page 4, lines 17-24, page 13, lines 12-20). The WO 94/01560 document teaches said polypeptides have epitope regions with positivity indices of at least about 100 (especially page 28, lines 19-32) and teaches that positivity index for a peptide is determined by multiplying the mean T cell stimulation index by the percent of individuals in a population sensitive to allergen (preferably at least 15 individuals), who have a T cell stimulation index to such peptide of at least 2.0. The WO 94/01560 document teaches that stimulation index for T cells to peptides can be calculated as the maximum CPM in response to a peptide divided by the control CPM (especially page 28, lines 2-5). WO 94/01560 teaches that peptides are selected based upon various factors including the frequency of the T cell response to the peptide in a population of individuals sensitive to the allergens and the strength of the T cell response to the peptide. It also teaches pharmaceutical compositions containing these polypeptides which comprise a sufficient percentage of the T cell epitopes such that at least about 60% of the T cell reactivity of the allergens are included in the composition. WO 94/01560 teaches that charged amino acid pairs such as KK or RR can be introduced between T cell epitope regions and that the resulting peptide is rendered sensitive to capthepsin and/or other trypsin-like enzymes which are involved in processing of T cell epitopes in vivo (especially page 24, lines 5-13). WO 94/01560 teaches peptides comprising at least two regions, each region comprising at least two T cell epitopes of a Japanese cedar pollen protein allergen or comprising epitopes from peptides which are immunologically related (especially page 26, lines 25-31). The WO 94/01560 document also teaches a method for determining which peptides from cry j 1 or another allergen have T cell epitope regions (especially page 27, lines 19-32 and continuing onto page 28, lines 1-5).

Hashiguchi et al teach T cell epitopes of Cry j 2.

WO 94/11512 teaches purified Cry j 2 protein, and T cell epitopes thereof, a method of producing the protein and epitopes and a method of identifying T cell epitopes, and the usefulness in treatment, diagnosing and preventing Japanese cedar pollinosis (especially Abstract, page 14, lines 35-36 and continuing onto page 15, lines 1-6 and lines 17-37 and page 16, lines 1-36).

Komiyama et al teach the deduced amino acid sequence of Cry j 2, the second major allergen of Japanese Cedar Pollen, Cry j 1 being the first (especially Abstract and page 1021 and first paragraph of page 1022). Komiyama et al teach that amino acid sequence information for Cry j 2 is useful for the determination of T cell epitopes from that allergen (especially page 1027, lines 3-8). Komiyama et al teach that patients suffering from pollinosis have IgE antibodies specific for Cry j 1 and Cry j 2 (especially page 1022, lines 7-8) and the usefulness of recombinant Cry j 2 protein for immunotherapy (especially page 1027, lines 8-10).

Wallner et al teach that the diversity of the human population with respect to its HLA haplotype has to be taken into account in defining clinical peptide candidates. Wallner et al teach that permissive interaction between peptides and several HLA alleles probably accounts for the observation that peptides containing the major T-cell epitope of an allergen cause T-cell responses in 80-90% of the allergic population and that clinical peptide candidates therefore have to be designed to cover the diverse HLA haplotype of the allergic patient population.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have arrived at the claimed invention: given the teaching of Rogers et al of a linear multi-epitope linear polypeptide with different T cell regions from an allergen joined together and wherein the peptide does not substantially react with IgE antibodies of the population of patients sensitive to said allergen, each of said T cell epitopes shows a positivity index of not less than approximately 100, and wherein said peptide reacts with peripheral lymphocytes from at least not less than 70% of said population of patients sensitive to said allergen and given the teaching that said peptide can be constructed using T cell epitopes from allergens from diverse sources; given the teaching of WO 94/01560 of linear peptides comprising at least two different T cell epitopes from Cry j 1 joined together or from peptides that are immunologically related, and the teaching that lysine or arginine dimers can be introduced between T cell epitope regions to serve as the site that is processed in antigen-presenting cells; given the teaching of Hashiguchi et al of T cell epitopes from Cry j 2 or the teaching of Komiyama et al of the deduced amino acid sequence of Cry j 2, a second major allergen of Japanese Cedar Pollen and the usefulness of this information for the determination of T cell epitopes from Cry j 2, or the teaching of WO 94/11512 of cry 2 protein and a method for identifying T cell epitopes.

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the T cell epitope regions from Cry j 1 and Cry j 2 for the T cell epitopes of Fel d I in the invention of Rogers et al given the teaching of WO 94/01560 of linear peptides comprising at least two different T cell epitopes from Cry j 1 joined together or from peptides that are immunologically related and given the teaching of Hashiguchi et al of T cell epitopes from Cry j 2 or the teaching of Komiyama et al of the deduced amino acid sequence of Cry j 2, a second major allergen of Japanese Cedar Pollen, the usefulness of this information for the determination of T cell epitopes from Cry j 2, that patients suffering from pollinosis have IgE antibodies specific for Cry j 1 and Cry j 2 and the usefulness of recombinant Cry j 2 protein for immunotherapy, or the teaching of WO 94/11512 of Cry j 2 protein, and T cell epitopes thereof, a method of producing the protein and epitopes and a method of identifying T cell epitopes, and the usefulness in treatment, diagnosing and preventing Japanese cedar pollinosis, particularly in light of the teaching of Rogers et al that their approach to a peptide-based immunotherapeutic agent can be generally applicable to the combination of multiple T cell epitope-containing sequences from one or more antigens into a single polypeptide chain, that a single antigen can have multiple T cell epitopes recognized in the atopic human population, and that the polypeptide can also be constructed using T cell epitopes from unrelated antigens or allergens from diverse sources. Claim 7 is included because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to create a peptide-based immunotherapeutic agent that contains an epitope restricted by an HLA molecule that is frequent in different ethnic groups being targeted, as taught by Wallner et al.

From the reference teachings, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because immunotherapeutic agents comprising multi-epitope peptides that have the useful characteristics recited in instant claims 1, 4 and 5 were known in the art and because the approach to said peptide-based immunotherapeutic agents were known to be generally applicable to other allergens besides Fel d I, because multi-epitope peptides of Cry j 1 were in use at the time the invention was made and because Cry j 2 was known to be a second major allergen of Japanese Cedar pollinosis and the T cell epitopes were known or could be deduced through use of methods commonly in use at the time the invention was made. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Upon consideration of a sequence search, SEQ ID NO: 1 is free of the prior art.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the in the specification.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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